47. (Amended) An antibody or fragment thereof which is raised against at least a portion of a polypeptide comprising SEQ ID NO: 11, wherein the portion is not identical to any portion of Cek5.

REMARKS

Claims 28, 29, 31, 36-56 are pending in the application, of which claims 38-46 are currently under consideration. Applicants enclose an appendix showing the changes made to claim 47. Support for the proposed amendment to claim 47 can be found in the specification, e.g., at page 4, lines 20-21. The Manual of Patent Examining Procedure (MPEP) indicates that a negative limitation in a claim is supported by a positive recitation of that limitation in the specification. MPEP § 2173.05(i). Thus, positive recitation of Cek5 in the specification supports the negative limitation in amended claim 47. Applicants submit that the proposed amendment of claim 47 does not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner. It also places the application in better condition for allowance or appeal. Thus, entry of the amendment is respectfully requested. Applicants respectfully request reconsideration and withdrawal of all outstanding rejections.

Drawings

The Examiner objected to the drawings for the reasons indicated in the Notice of Draftperson's Patent Drawing Review Form PTO-948 attached to the Office Action mailed September 25, 2001. Action at page 2, item no. 3. The Examiner required corrected drawings and stated that the objection will not be held in abeyance. *Id.*

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Applicants enclose 33 sheets of formal drawings (Figures 1-11) and request that the informal drawings be replaced with those formal drawings. If the formal drawings are not in full compliance with the pertinent statutes and regulations for any reason, please so advise the undersigned. The formal drawings add no new matter.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 43, 46, 51, and 56 under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Action at page 3, item no. 5. The Examiner alleged that "[t]he claims require a pharmaceutical composition yet the specification does [*sic*] provide sufficient guidance as to what the antibody is therapeutically effective for; and neither can such a use be reasonably inferred from the prior art, as set forth previously." *Id.* Applicants assume that the Examiner intended to allege that "the specification does *not* provide sufficient guidance as to what the antibody is therapeutically effective for..." and will respond to the rejection accordingly. The Examiner further alleged that "[t]he term 'pharmaceutical composition' implicitly requires that the composition be used for some form of treatment or therapy." Action at pages 3 and 4.

Applicants respectfully traverse. Each of the rejected claims recites "[a] pharmaceutical composition comprising an antibody of claim [38, 42, 47, or 52] in a mixture with a pharmaceutically acceptable adjuvant, carrier, solubilizer, or diluent." The Manual of Patent Examining Procedure (MPEP) states that

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> [i]f the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction.

MPEP § 2111.02. Applicants assert that the body of the claim sets forth all of the limitations of the claimed invention and that the term 'pharmaceutical composition' in the preamble merely states a purpose or intended use of the invention, and is therefore not a limitation of the claim.

Furthermore, applicants assert that the term 'pharmaceutical composition' does *not* implicitly require "that the composition be used for some form of treatment or therapy." Such a composition may be used, e.g., for diagnosis *in vivo*. Compositions used for diagnosis may also be referred to as pharmaceutical compositions because they comprise pharmaceutically acceptable adjuvants, carriers, solubilizers, or diluents.

Thus, applicants assert that the phrase 'pharmaceutical composition' merely states a purpose or intended use of the invention and does *not* require that the composition be used as a treatment or therapy. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 43, 46, 51, and 56 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 47 and 52 under 35 U.S.C. § 102(b) as allegedly being anticipated by Pasquale EB (1991) *Cell Regulation*, 2(7): 523-534 (Pasquale). Action at page 4, item no. 7. The Examiner alleged that "as Cek5 and the instant Hek5 contain more portions in common with each other than portions that are different, the Pasquale antibodies were raised against a portion of Hek5." *Id.* The Examiner further

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alleged that "Pasquale teach every element of certain embodiments of generic claims 47 and 52 because the claims only require that the antibodies be raised against a portion of Hek5, as discussed above." Action at pages 4 and 5.

Applicants respectfully traverse. Solely to expedite prosecution and without acquiescing to the rejection, applicants propose to amend claim 47 to recite "[a]n antibody or fragment thereof which is raised against at least a portion of a polypeptide comprising SEQ ID NO: 11, wherein the portion is not identical to any portion of Cek5." Claim 52 recites "[a]n antibody or fragment thereof which is raised against at least a portion of amino acids 1 to 524 of SEQ ID NO: 11."

In order to anticipate a claim, a reference must teach every element of that claim. MPEP § 2131. Pasquale discusses antibodies raised against a protein consisting of amino acids 167-926 of Cek5 fused to β-galactosidase. *See* Pasquale at page 525, right column, to page 526, left column. Those antibodies cannot anticipate claim 47, because the protein consisting of amino acids 167-926 of Cek5 differs from Hek5 at several positions. Thus, those antibodies were not "raised against at least a portion of a polypeptide comprising SEQ ID NO: 11," which is the amino acid sequence of Hek5. Those antibodies also cannot anticipate claim 52, because amino acids 167-926 of Cek5 art not "at least a portion of amino acids 1 to 524 of SEQ ID NO: 11."

Pasquale also discusses antibodies raised against a peptide consisting of the last 10 amino acids of Cek5. *Id.* Those antibodies cannot anticipate claim 47, because the peptide consisting of the last 10 amino acids of Cek5 is not "at least a portion of a polypeptide comprising SEQ ID NO: 11, wherein the portion is not identical to any portion of Cek5." Those antibodies also cannot anticipate claim 52, because the last

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ten amino acids of Cek5 correspond to amino acids 961 to 970 of Hek5 and therefore are not "at least a portion of amino acids 1 to 524 of SEQ ID NO: 11."

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 47 and 52 under 35 U.S.C. § 102(b).

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 38-42, 44, 45, 48-50, and 53-55 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pasquale, as applied to claims 47 and 52, in view of U.S. Patent No. 4,816,567 (the '567 patent). Action at page 5, item no. 9. The Examiner alleged that the '567 patent "teaches that in the art of antibody production, monoclonal antibodies are generally preferred to polyclonal antibodies, while CDR grafted and otherwise chimeric antibodies are more preferred." *Id* (citations omitted).

Applicants respectfully traverse and incorporate by reference the arguments made in the Amendment and Response filed September 3, 2002. Applicants will first discuss the rejection with respect to the rejected monoclonal antibody claims, which are claims 38-42, 44, and 45. Applicants will then discuss the rejection with respect to the remaining claims, claims 48-50 and 53-55.

Claim 38 recites

> [a] monoclonal antibody or fragment thereof that binds a polypeptide consisting of an amino acid sequence selected from:
> (a) amino acids 1 to 524 of SEQ ID NO: 11,
> (b) amino acids 1 to 547 of SEQ ID NO: 13, and
> (c) amino acids 1 to 547 of SEQ ID NO: 15.

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Claims 39, 40, and 41 depend from claim 38. Claim 42 recites "[a] monoclonal antibody or fragment thereof that binds a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 11." Claims 44 and 45 depend from claim 42.

The Examiner alleged that "it would be obvious to one of ordinary skill in the art at the time the invention was made, with reasonable expectation of success, to make a monoclonal, chimeric, or CDR grafted antibodies according to U.S. Patent No. 4816567 when practicing the invention of Pasquale EB." *Id.*

Pasquale, however, only discusses the chicken protein Cek5. Applicants assert that if one skilled in the art had made the modification of Pasquale suggested by the Examiner, he would have produced monoclonal, chimeric, or CDR grafted antibodies to the *chicken protein Cek5*, not to the human protein Hek5. Nowhere in Pasquale did the authors teach or suggest the human protein Hek5. Applicants therefore assert that Pasquale does not teach and would not have suggested an antibody or fragment thereof that "binds a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 11," which is the sequence of the human protein Hek5 (claim 42). Pasquale also does not teach and would not have suggested an antibody or fragment thereof that "binds a polypeptide consisting of...amino acids 1 to 524 of SEQ ID NO: 11..." (claim 38). Furthermore, the '567 patent fails to remedy the deficiencies of Pasquale. Therefore, applicants assert that the Examiner failed to establish that the combination of Pasquale and the '567 patent would have suggested monoclonal antibodies or fragments according to any of claims 38-42, 44, and 45. Moreover, applicants need not address the Examiner's contentions concerning the combination of

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Pasquale and the '567 patent with respect to other elements of certain claims. By not addressing those contentions, applicants in no way acquiesce to those contentions.

Applicants now address the rejection with respect to claims 48-50 and 53-55. Claims 48, 49, and 50 depend from claim 47. Solely to expedite prosecution and without acquiescing to the rejection, applicants propose to amend claim 47 to recite "[a]n antibody or fragment thereof which is raised against at least a portion of a polypeptide comprising SEQ ID NO: 11, wherein the portion is not identical to any portion of Cek5." Claims 53, 54, and 55 depend from claim 52. Claim 52 recites "[a]n antibody or fragment thereof which is raised against at least a portion of amino acids 1 to 524 of SEQ ID NO: 11."

For at least the reasons set forth above for the 35 U.S.C. § 102(b) rejection, applicants assert that Pasquale fails to teach and would not have suggested: (1) "[a]n antibody or fragment thereof which is raised against at least a portion of a polypeptide comprising SEQ ID NO: 11, wherein the portion is not identical to any portion of Cek5" (claim 47, from which claims 48-50 depend); or (2) "[a]n antibody or fragment thereof which is raised against at least a portion of amino acids 1 to 524 of SEQ ID NO: 11" (claim 52, from which claims 53-55 depend). The '567 patent does not remedy the deficiencies of Pasquale. Thus, applicants assert that the Examiner has failed to establish that the combination of Pasquale and the '567 patent would have suggested every element of claims 48-50 and 53-55. Therefore, the Examiner failed to establish that those claims would have been obvious over Pasquale and the '567 patent. Moreover, applicants need not address the Examiner's contentions concerning the combination of Pasquale and the '567 patent with respect to other elements of certain

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claims. By not addressing those contentions, applicants in no way acquiesce to those contentions.

In conclusion, applicants assert that the Examiner has failed to establish that the combination of Pasquale and the '567 patent would have rendered obvious claims 38-42, 44, 45, 48-50, and 53-55. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Pasquale in view of the '567 patent.

The Examiner rejected claims 42, 44, 45, 47-50 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Iwase et al. (1993) *Biochem. Biophys. Res Comm.*, 194(2): 698-705 (Iwase) in view of the '567 patent for the reasons set forth in the previous Office Action. Action at page 6, item no. 10. The Examiner alleged that Iwase teaches

> that the polypeptide (H1) is dramatically up regulated in human gastric cancers and the dysregulation of the expression of the polypeptide is probably involved in the development of these gastric cancers. Iwase et al. do not specifically discuss antibodies to the polypeptide, however it is well appreciated by one of ordinary skill in the art that such antibodies would be useful for diagnosis of gastric cancers as taught by Iwase et al.

Id.

Applicants traverse. As discussed above, claim 42 recites "[a] monoclonal antibody or fragment thereof that binds a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 11." Claims 44 and 45 depend from claim 42. As discussed above, claim 47 recites "[a]n antibody or fragment thereof which is raised against at least a portion of a polypeptide comprising SEQ ID NO: 11, wherein the portion is not identical to any portion of Cek5." Claims 48-50 depend from claim 47.

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First, applicants assert that Iwase does *not* teach that "the polypeptide (H1) is dramatically up regulated in human gastric cancers." Nowhere in Iwase do the authors assert that the H1 polypeptide is upregulated. Rather, Iwase discusses only the upregulation of the H1 mRNA or the H1 gene. It is well known in the art that upregulation of an mRNA or a gene does not necessarily correlate with upregulation of a polypeptide. In fact, Iwase carefully avoids making the statement that the H1 polypeptide itself is upregulated. Instead, he states that "expression of [H1] mRNA was extremely higher in cancer tissues than in normal stomach in all cases examined." Iwase at page 703.

Furthermore, Iwase teaches a method for detecting the upregulation of H1 mRNA using Northern blot analysis, in which the level of mRNA in a cell is detected using radiolabeled polynucleotide probes. Applicants assert that Northern blot analysis of mRNA is fundamentally different from using an antibody to detect a protein. Applicants therefore assert that Iwase does not teach and would not have suggested using antibodies to detect the Hek5 protein.

Second, applicants assert that the Office is obligated to present a factual showing of the teaching or motivation to combine references. The Examiner merely alleged that "it is well appreciated by one of ordinary skill in the art that such antibodies would be useful for diagnosis of gastric cancers as taught by Iwase et al." Action at page 6. In reversing the Board of Appeals in *In re Lee*, 277 F.3d 1338, 61 USPQ2d 1430 (2002), the Federal Circuit reiterated that

> our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to

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> combine prior art references. . . . This precedent has been reinforced in myriad decisions, and cannot be dispensed with.

Id. at 1343.

Thus, the Examiner must identify the specific motivation for combining Iwase and the '567 patent to suggest antibodies or fragments thereof that bind to Hek5. Iwase dicusses the use of Northern blots to detect upregulation of H1 mRNA in gastric cancers and never suggests the use of antibodies. Applicants assert that the Examiner has failed to identify the specific motivation for combining those references and therefore has failed to set forth a *prima facie* case of obviousness.

Finally, the Examiner alleged that "[t]he skilled artisan would expect that the production of antibodies against H1 would necessarily involve portions of H1 identical to portions of SEQ ID NO: 11." Action at page 7. For at least the reasons set forth above, applicants assert that the Examiner has failed to identify a specific motivation for combining Iwase and the '567 patent to produce antibodies against H1. Thus, applicants need not address the Examiner's contentions with respect to whether one skilled in the art would expect "that the production of antibodies against H1 would necessarily involve portions of H1 identical to portions of SEQ ID NO: 11." By not addressing those contentions, applicants in no way acquiesce to those contentions.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 42, 44, 45, 47-50 under 35 U.S.C. § 103(a) over Iwase in view of the '567 patent.

Applicants respectfully request that this Amendment and Response be considered by the Examiner. Applicants respectfully assert that the present application is in condition for allowance and request that the Examiner issue a timely Notice of

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Allowance. If the Examiner does not consider the application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6656 to set up at interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: February 14, 2003

By: _____
Rebecca B. Scarr
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Serial No.: 09/378,759
Filed: August 23, 1999
Attorney Docket No. 6843.0027-03000

APPENDIX TO AMENDMENT AND RESPONSE

Version with Markings to Show Changes Made

IN THE CLAIMS:

Changes made to claim 47:

47. (Amended) An antibody or fragment thereof which is raised against at least a portion of a polypeptide comprising SEQ ID NO: 11, wherein the portion is not identical to any portion of Cek5.

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